US cases

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
GREGORY A. HUNT
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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 27 JUN 2008
Applicant's or agent's file reference 180/157/2/2/2 PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 07/26493	International filing date *(day/month/year)* 31 December 2007 (31.12.2007)
Applicant DUKE UNIVERSITY	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT-Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

VJLL 7/1/08

DOCKET DATES: 7/27; 8/27/08
ASSIGNED ATTY: AAT
FILE NO. 180/157/2/2/2 PCT
DOCKETED BY: PAR DATE: 7/2/08

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 180/157/2/2/2 PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 07/26493	International filing date *(day/month/year)* 31 December 2007 (31.12.2007)	(Earliest) Priority Date *(day/month/year)* 29 December 2006 (29.12.2006)
Applicant DUKE UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 4

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☒ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/26493

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I, claims 1-14, drawn to a method of predicting efficacy of a treatment in a subject, the method comprising:
-- monitoring accumulation of a compound of interest at a desired site in vivo by magnetic resonance imaging; and
-- predicting efficacy of treatment based on accumulation of a compound of interest at the desired site.

Group II, claims 15-53, drawn to a method of enhancing efficacy of a treatment at a desired site in a subject, the method comprising:
-- administering to the subject a composition comprising a compound of interest; and
-- targeting the composition to a desired location.

********** SEE SUPPLEMENTAL SHEET TO CONTINUE **********

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/26493

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 51/00 (2008.04)
USPC - 424/1.21; 977/702
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 424/1.21; 977/702
IPC(8): A61K 51/00 (2008.04)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/486

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, CRISP, PUBMED, Google Scholar: accumulat$4 near5 (compound or medica$4 or drug or chemic$4) and efficac$4 and (mri or magnetic adj resonan$4) and chemotherap$6 and liposome near10 (contrast) and DSPC and contrast adj agent and envirosensitive near5 liposome and (thermosensitive or chemosensitive or radiation)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2004/0101969 A1 (VIGLIANTI et al.) 27 May 2004 (27.05.2004); para [0013]-[0021], [0063], [0101]-[0108], [0113], [0114], [0123], [0165], [0209]; Claim 28	1-29, 31- 48 and 50-53 --- 30 and 49
Y	US 2005/0136002 A1 (FOSSHEIM et al.) 23 Jun 2005 (23.06.2005); para [0061], [0066] and [0149]	30 and 49

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2008 (19.06.2008)	27 JUN 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

International application No.
PCT/US 07/26493

********** SUPPLEMENTAL SHEET **********

In continuation of BOX III Observations where unity of invention is lacking (Continuation of item 3 of first sheet):

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group II does not include the inventive concept of monitoring accumulation of a compound of interest at a desired site in vivo by magnetic resonance imaging and predicting efficacy of treatment based on accumulation of a compound of interest at the desired site, as required by Group I.

Groups I and II do share the technical feature of administering to the subject a composition comprising a compound of interest; and targeting the composition to a desired location. However, this shared technical feature does not represent a contribution over the prior art of US 2004/0115186 A1 to SEGAL et al, which teaches a method of enhancing the effectiveness of anti-tumor compounds (abstract) by employing liposomes having an active agent in entrapped form, and outer surfaces of the liposome include a cell targeting moiety effective to bind specifically to a target surface (para [0150]). Since the above steps of administering and targeting were known at the time of the invention, as evidenced by the teaching of SEGAL, they cannot be considered a special technical feature that would otherwise unify the groups.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
GREGORY A. HUNT
JENKINS WILSON, TAYLOR & HUNT, P.A.
SUITE 1200, UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM, NC 27707

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 27 JUN 2008	
Applicant's or agent's file reference 180/157/2/2/2 PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 07/26493	31 December 2007 (31.12.2007)	29 December 2006 (29.12.2006)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 51/00 (2008.04)
USPC - 424/1.21; 977/702

Applicant DUKE UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	19 June 2008 (19.06.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/26493

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/26493

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

Group I, claims 1-14, drawn to a method of predicting efficacy of a treatment in a subject, the method comprising:
-- monitoring accumulation of a compound of interest at a desired site in vivo by magnetic resonance imaging; and
-- predicting efficacy of treatment based on accumulation of a compound of interest at the desired site.

Group II, claims 15-53, drawn to a method of enhancing efficacy of a treatment at a desired site in a subject, the method comprising:
-- administering to the subject a composition comprising a compound of interest; and
-- targeting the composition to a desired location.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group II does not include the inventive concept of monitoring accumulation of a compound of interest at a desired site in vivo by magnetic resonance imaging and predicting efficacy of treatment based on accumulation of a compound of interest at the desired site, as required by Group I.

Groups I and II do share the technical feature of administering to the subject a composition comprising a compound of interest; and targeting the composition to a desired location. However, this shared technical feature does not represent a contribution over the prior art of US 2004/0115186 A1 to SEGAL et al, which teaches a method of enhancing the effectiveness of anti-tumor compounds (abstract) by employing liposomes having an active agent in entrapped form, and outer surfaces of the liposome include a cell targeting molety effective to bind specifically to a target surface (para [0150]). Since the above steps of administering and targeting were known at the time of the invention, as evidenced by the teaching of SEGAL, they cannot be considered a special technical feature that would otherwise unify the groups.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos. _____

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/26493

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	30 and 49	YES
	Claims	1-29, 31-48 and 50-53	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-53	NO
Industrial applicability (IA)	Claims	1-53	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-29, 31- 48 and 50-53 lack novelty under PCT Article 33(2) as being anticipated by US 2004/0101969 A1 to Viglianti et al. (hereinafter 'Viglianti').

A to claim 1, Viglianti teaches a method of predicting efficacy of a treatment in a subject, the method comprising:
monitoring accumulation of a compound of interest at a desired site in vivo by magnetic resonance imaging (para [0113], [0209]); and
predicting efficacy of treatment based on accumulation of a compound of interest at the desired site (para [0113], [0209]).

As to claim 2, Viglianti further teaches the method wherein the compound of interest is a chemotherapeutic agent (para [0113], [0209]).

As to claim 3, Viglianti further teaches the method comprising:
administering to a subject a non-sensitive liposome composition (para [0013]) comprising:
(i) a contrast agent (para [0013]);
(ii) a compound of interest (para [0013]); and
(iii) a non-sensitive liposome encapsulating the contrast agent and the compound of interest (para [0013]); and
monitoring the accumulation of the compound of interest at the desired site by magnetic resonance imaging (para [0013]).

As to claim 4, Viglianti further teaches the method wherein the non-sensitive liposome comprises DSPC/Cholesterol (55:45, mol:mol) (para [0020]).

As to claim 5, Viglianti further teaches the method wherein the contrast agent comprises an element selected from the group consisting of Gd, Cu, Cr, Fe, Co, Er, Ni, Eu, Dy, Zn, Mg, Mo, Li, Ta, and Mn (para [0020]).

As to claim 6, Viglianti teaches the method further comprising:
administering an envirosensitive liposome composition to a subject (para [0016]-[0017]), the composition comprising:
(i) a contrast agent (para [0016]-[0017]);
(ii) a compound of interest (para [0016]-[0017]); and
(iii) an envirosensitive liposome encapsulating the contrast agent and the compound of interest (para [0016]-[0017]); and
monitoring the accumulation of the compound of interest at the desired site by magnetic resonance imaging (para [0016]-[0017]).

As to claim 7, Viglianti further teaches the method wherein the envirosensitive liposome is a thermosensitive liposome (para [0017]).

As to claim 8, Viglianti further teaches the method wherein the thermosensitive liposome comprises a formulation selected from the group consisting of DPPC-15 PEG2000, DPPC-DSPE-PEG2000(9 5:5, mol:mol), and DPPC-MSPC-DSPEPEG2000(0:10:4, mol:mol) (para [0020]).

As to claim 9, Viglianti further teaches the method wherein the contrast agent comprises a element selected from the group consisting of Gd, Cu, Cr, Fe, Co, Er, Ni, Eu, Dy, Zn, Mg, Mo; Li, Ta, and Mn (para [0021]).

As to claims 10 and 11, Viglianti further teaches the method further comprising exposing the envirosensitive liposome at the desired site to a non-physiological environmental condition (para [0018], [0063]), and wherein the environmental condition is hyperthermia (para [0018], [0063]), respectively.

As to claim 12, Viglianti further teaches the method wherein the desired site is a tumor, an injury site, and a tissue edema (para [0018]).

As to claim 13, Viglianti further teaches the method wherein the monitoring the accumulation of the compound of interest at the desired site by magnetic resonance imaging comprises making a pixel density determination (para [0108], [0123]; Claim 28).

As to claim 14, Viglianti further teaches the method wherein the predicting efficacy comprises predicting efficacy of treatment based on a location of accumulation at the desired site (para [0113]-[0114]).

**********Continued in Supplemental Box**********

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box V(2): Citations and Explanations:

As to claim 15, Viglianti teaches a method of enhancing efficacy of a treatment at a desired site in a subject, the method comprising:
administering to the subject a composition comprising a compound of interest (para [0105]-[0106]; and
targeting the composition to a desired location at a desired site in the subject, at a desired rate of accumulation at the desired site, to thereby enhance efficacy of treatment provided by the compound of interest (para [0116]).

As to claim 16, Viglianti further teaches the method wherein the compound of interest is a chemotherapeutic agent (para [0113], [0209]).

As to claim 17, Viglianti further teaches the method wherein the composition comprises a non-sensitive liposome composition comprising:
(i) the compound of interest (para [0013]); and
(ii) a non-sensitive liposome encapsulating the compound of interest (para [0013]).

As to claim 18, Viglianti further teaches the method wherein the non-sensitive liposome comprises DSPC/Cholesterol (55:45, moi:mol) (para [0020]).

As to claims 19 and 20, Viglianti further teaches the method wherein the composition further comprises a contrast agent (para [0013], and wherein the contrast agent comprises a element selected from the group consisting of Gd, Cu, Cr, Fe, Co, Er, Ni, Eu, Dy, Zn, Mg, Mo, Li, Ta, and Mn (para [0021]), respectively.

As to claims 21 and 22, Viglianti further teaches the method wherein the composition comprises an envirosensitive liposome composition (para [0016]-[0017]) comprising:
(I) the compound of interest (para [0016]-[0017]); and
(ii) an envirosensitive liposome encapsulating the compound of interest (para [0016]-[0017]), and, wherein the envirosensitive liposome is a thermosensitive liposome (para [0016]-[0017]), respectively.

As to claim 23, Viglianti further teaches the method wherein the thermosensitive liposome comprises a formulation selected from the group consisting of DPPCPEG2000, DPPC-DSPE-PEG2000 (95:5, mol:mol), and DPPC-MSPC-DSPE (90: 1 0:4, mol:mol) (para [0020]).

As to claim 24, Viglianti further teaches the method wherein the composition further comprises a contrast agent (para [0013]).

As to claim 25, Viglianti further teaches the method wherein the contrast agent comprises a element selected from the group consisting of Gd, Cu, Cr, Fe, Co, Er, Ni, Eu, Dy, Zn, Mg, Mo, Li, Ta, and Mn (para [0021]).

As to claim 26, Viglianti further teaches the method wherein a non-physiological environmental condition is present at the desired site, and the composition is targeted to a desired location at the desired site in the subject (para [0113]-[0114]).

As to claims 27 and 28, Viglianti further teaches the method wherein the non-physiological environmental condition is hyperthermia (para [0018], [0063]), and wherein the hyperthermia is provided by contacting a heated material with the desired site (para [0018]), respectively.

As to claim 29, Viglianti further teaches the method wherein the desired site is exposed to a non-physiological environmental condition before administering the composition (para [0101]-[0102]).

As to claim 31, Viglianti further teaches the method wherein the desired site is a tumor, an injury site, and a tissue edema (para [0018]).

As to claims 32 and 33, Viglianti teaches the method further comprising monitoring accumulation of the compound of interest at the desired site in vivo by magnetic resonance imaging (para [0113], [0209]), and wherein the monitoring the accumulation of the compound of interest at the desired site by magnetic resonance imaging comprises making a pixel density determination (para [0108], [0123]; Claim 28), respectively.

As to claim 34, Viglianti teaches the method further comprising predicting efficacy of treatment based on a location of accumulation at the desired site (para [0113]-[0114]).

As to claim 35, Viglianti teaches a method of targeting delivery of a compound of interest at a desired site in vivo, the method comprising:
administering to a subject a composition comprising a compound of interest (para [0016]-[0017]), wherein a non-physiological environmental condition is present at the desired site, and the composition is targeted to a desired location at the desired site in the subject (para [0113]-[0114]).

As to claim 36, Viglianti further teaches that the compound of interest is a chemotherapeutic agent (para [0113], [0209]).

As to claims 37-39, Viglianti further teaches the method wherein the composition comprises a non-sensitive liposome composition (para [0013]) comprising:
(I) the compound of interest (para [0013]); and
(ii) a non-sensitive liposome encapsulating the compoundof interest (para [0013]), and
wherein the non-sensitive liposome comprises DSPCICholesterol (5545, mol:mol) (para [0020], and
wherein the composition further comprises a contrast agent (para [0013]), respectively.

As to claim 40, Viglianti further teaches the method wherein the contrast agent comprises an element selected from the group consisting of Gd, Cu, Cr, Fe, Co, Er, Ni, Eu, Dy, Zn, Mg, Mo, Li, Ta, and Mn (para [0021]).

**********Continued in Supplemental Box**********

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V(2): Citations and Explanations and the preceding Supplemental Box:

As to claims 41 and 42, Viglianti further teaches the method wherein the composition comprises an envirosensitive liposome composition (para [0016]-[0017]) comprising:
(i) the compound of interest (para [0016]-[0017]); and
(ii) an envirosensitive liposome encapsulating the compound of interest (para [0016]-[0017]), and
wherein the envirosensitive liposome is a thermosensitive liposome (para [0017]), respectively.

As to claim 43, Viglianti further teaches the method wherein the thermosensitive liposome comprises a formulation selected from the group consisting of DPPC-15 PEG2000D, PPC-DSPE-PEG2000(95:5, mol:mol), and DPPC-MSPC-DSPEPEG2000 (90:10:4, mol:mol) (para [0020]).

As to claim 44, Viglianti further teaches the method wherein the composition further comprises a contrast agent (para [0016]-[0017]).

As to claim 45, Viglianti further teaches the method wherein the contrast agent comprises an element selected from the group consisting of Gd, Cu, Cr, Fe, Co, Er, Ni, Eu, Dy, Zn, Mg, Mo, Li, Ta, and Mn (para [0021]).

As to claims 46 and 47, Viglianti further teaches the method wherein the non-physiological environmental condition is hyperthermia (para [0018], [0063]), and wherein the hyperthermia is provided by a contacting a heated material with the desired site (para [0018]), respectively.

As to claim 48, Viglianti further teaches the method wherein the desired site is exposed to a non-physiological environmental condition before administering the composition (para [0101]-[0102]).

As to claim 50, Viglianti further teaches the method wherein the desired site is a tumor, an injury site, and a tissue edema (para [0018]).

As to claim 51, Viglianti teaches the method further comprising monitoring accumulation of the compound of interest at the desired site in vivo by magnetic resonance imaging (para [0016]-[0017]), and wherein the monitoring the accumulation of the compound of interest at the desired site by magnetic resonance imaging comprises making a pixel density determination (para [0108], [0123]; Claim 28).

As to claim 53, Viglianti teaches the method further comprising predicting efficacy of treatment based on a location of accumulation at the desired site (para [0113]-[0114]).

Claims 30 and 49 lack inventive step under PCT Article 33(3) as being obvious over Viglianti, as above, in view of US 2005/0136002 A1 to Fossheim et al. (hereinafter 'Fossheim').

As to claims 30 and 49, Viglianti does not specifically teach administering the composition in one or more patial doses. Fossheim teaches a method for delivering a composition using MRI-imageable liposomes (para [0061], [0066]) and further comprising administering the composition in one or more partial doses (para [0149]). It would have been obvious to one having ordinary skill in the art to combine the teachings of Viglianti and Fossheim to achieve a method for administration of a composition having lower toxicity because Viglianti teaches that targeting allows for administration of a composition at lower quantities (para [0165]). In addition, Viglianti teaches the method wherein the desired site is exposed to a non-physiological environmental condition before administering the composition (para [0101]-[0102]).

Claims 1-53 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.